REMARKS

Claims 1 – 24 are pending in the application. Claims 1, 6, 10, 11, 12, 14 and 16 have been amended as describe in detail below.

The specification has been amended to include the number of the issued U.S. Patent equivalent to WO93/7178.

Rejections pursuant to 35 U.S.C. § 112, second paragraph

Claims 1 and 16, and each of the claims depending therefrom, stand rejected as indefinite due to the use of the term "derived from." Since claim 16 does not use the term "derived from," Applicant assumes the rejection is directed to claim 14. Claims 1 and 14 have been amended to remove this term. Support for this amendment can be found throughout the Specification and including, for example, page 7, lines 5 – 11 and page 10, lines 26 – 35 (the latter passage having been amended herein to provide the number of the U.S. patent that issued from the application published as WO 93/7178).

The amendment is not intended to change the scope of the claims but to simply provide an alternative description of the invention. The specification discusses that the polysaccharides conjugated to the carrier proteins are extracted from *S. pneumoniae* by conventional methods and purified according to conventional methods. The polysaccharides may be used in crude form or, alternatively, the polysaccharides may be fragmented in order to obtain polysaccharides having an average molecular weight less than that of the polysaccharides originally extracted. *See* Specification, p. 10, lines 26 – 35. Further, page 12, the paragraph beginning at line 10, explains that polysaccharides "derived from" various serotypes were fragmented according to known methods. (see lines 13-16). For coupling to a protein carrier, the polysaccharide is subjected to

reductive amination in the presence of sodium cyanoborohydride in order to link a molecule of diaminohexane to a terminal reducing group. The polysaccharide "thus derived" is then activated by a succinimide group. (lines 22-24). In another example, in the same paragraph, the polysaccharide is treated to add hydrazine groups. The polysaccharide "thus derived" is then coupled with the carrier protein in the presence of EDAC. All these polysaccharides are "from a *Streptococcus pneumoniae* serotype/serogroup" as the phrase is used in the claims.

With the amendment, Applicant is not disclaiming any of the embodiments obtained by conventional methods of obtaining, purifying, modifying and conjugating polysaccharides that are disclosed in the specification and known to those of skill in the art. With the amendment, Applicant respectfully submits that the amendment has been traversed.

Claim 6 and each of claims depending therefrom stand rejected as the Examiner is of the opinion that the acronyms "A1" and "A2" are indefinite. Applicants respectfully disagree. Claim 1 recites that the "carrier proteins P1 to Pn are selected independently from a group consisting of "m" carrier proteins Al to Am...." Claim 6 simply narrows the group to two different carrier proteins. The acronyms A1 and A2 are not intended to describe any specific carrier protein, but indicate that the carrier proteins P1 to Pm are selected from a group of two proteins. *See* Specification, p. 7, lines 31 - 34. Nevertheless, Applicant has amended claim 6 in a manner that obviates the rejection, yet maintains the scope of the claim. Given that claim 6 is clear and definite, Applicant respectfully requests that the rejection be withdrawn.

Claim 7 stands rejected as indefinite because, according to the Examiner, it is unclear what A1 and A2 represent, the claim is confusing, and the claim does not appear to limit claim 1. Applicant respectfully disagrees. Claim 7 clearly expresses the concept that, when the composition has two carrier proteins (A1 and A2), the amount of the proteins is balanced, *i.e.*

half (or about half) of the conjugates include A1, and the other half (or about half) includes A2. *See* Specification, p. 8, lines 28 – 38. Nevertheless, Applicants have amended the claim in a manner that obviates the rejection but maintains the scope of the claim.

Examiner asks how the carrier is both A1 and A2 at the same time. The answer is that one half of the conjugates (*i.e.* "n"/2) include first carrier protein and the other half of the conjugates include a second carrier protein. Thus, the phraseology " "n"/2 carrier proteins P1 to Pn are a first carrier protein and "n"/2 carrier proteins P1 to Pn are a second carrier protein..." is appropriate. When there is an odd number of conjugates (n is an odd number), the same principal applies, except just over one-half of the conjugates (("n"+1)/2) include the first carrier protein as the carrier protein, and just under one-half of the conjugates (("n"-1)/2) include the second carrier protein.

The Examiner asks if Applicant is intending to assign the even numbered "Pns" to A1 and the odd numbered "Pns" to A2. The answer is that is that it doesn't matter which are odd and which are even as long as, in the composition, one-half of carrier proteins are the first carrier protein and one-half are the second carrier protein (unless there is an odd number of conjugates (n is odd), where there is one more conjugate having the first carrier protein than the second carrier protein).

The Examiner is concerned that claim 7 does not further limit claim 1, and claim 1 requires at least one of the carrier proteins to be different from the others. Claim 7 does further limit claim 1 since it requires that one-half the proteins be the first protein and one-half be the second protein (unless n is odd, when there is one more conjugate having the first protein than the second protein).

For the above reasons, Applicant respectfully submits that claim 7 is clear and definite. Accordingly, Applicant requests that the rejection of claim 7 be withdrawn.

Claims 10 and 16, and the claims depending therefrom, stand rejected as unclear because, according to the Examiner, the claims are unclear because "Dt" alone is not part of the composition and the term "dose" lacks antecedent basis. Claims 11 and 16 are rejected for a similar reason as it applies to the term "Tt." With regard to the amount of the protein, the Examiner is correct that Dt or Tt ("the proteins") are not alone in the composition, but are conjugated to a polysaccharide. The Specification describes that amount of protein is calculated based upon the ratio of protein to polysaccharide in the conjugate. *See* specification, page 12, line 37 to page 14, line 10. Accordingly, Applicant respectfully submits that claims 10, 11 and 16 are clear. Also, to address the lack of antecedent basis for "dose," claims 10, 11 and 16 have been amended to provide an antecedent basis for "dose." Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Claim 12 stands rejected as confusing because of the language "comprises 10 or 11 valances represented by 10 or 11 conjugates." The Examiner asks what is the intended difference between valences and conjugates. "Valence" refers to one of the various serotypes/serogroups of polysaccharide. This is different than "conjugate" which refers to the combination of one of the polysaccharides (one of the valences) and a carrier protein. Thus, a valence is not a conjugate. In order to clarify the claim, Applicant has amended claim 12 claim to remove the term "valences." With this amendment, Applicant requests that the rejection be withdrawn.

Claim 14 stands rejected because according to the Examiner the claim is unclear since it does not use the terminology of claim 1 and it is not clear in its antecedent basis. Applicant has

amended to claim to use the terminology from claim 1. Applicant assumes this clarifies any antecedent basis as well. Accordingly, Applicant requests that this rejection be withdrawn.

Rejection pursuant to 35 U.S.C. § 103

Claims 1 – 24 stand rejected under 35 U.S.C. § 103 as *prima facie* obvious over Chu, *et al.,* Infection and Immunity, 40:245-56 (1983) (hereinafter "Chu *et al.*") in combination with Merck & Co. Inc., European Patent Application No. 0 497 525 A (hereinafter "EPA 0 497 525").

Chu *et al.* teach the use of up to three different polysaccharide/protein conjugates of *Haemophilus influenzae* type B (Hib), Pneumococcal Type 6A (Pn6A), and *E. Coli* H100 to potentially increase the immunogenicity of the Hib and Pn6A. The conjugates include the polysaccharides attached to either horseshoe crab hemocyanin (HCH) or Dt. EPA 0 497 525 teaches vaccines comprising a mixture of one to ten different *pneumococcal* polysaccharide-immunogenic protein conjugates (Pn-Ps-PRO) that induce a broadly protective recipient immune response. EPA 0 497 525 also teaches that the protein (PRO) portion of the conjugate may be an immune enhancer such as Tt or Dt (but not both).

With regard to claims 1 – 12 and 14, the Examiner asserts that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the conjugates of Chu *et al.* by combining any of the Pn-Ps-PRO of EPA 0 497 525 to provide for a vaccine containing up to ten different Pn-Ps-PRO conjugates. To establish a case of *prima facie* obviousness, the Examiner must show, *inter alia,* a motivation to combine the references.

Applicants respectfully disagree that either Chu *et al.* or EPA 0 497 525 provide any motivation to combine their teachings. The compositions of the present invention provide a multivalent vaccine that avoids the negative interference normally associated with such vaccines

by using at least two protein carriers so that the maximum load of each of the carriers is not reached. *See* Specification p. 4, lines 10 – 23. The Examiner points out that Chu *et al.* teach that when Hib-HCH was injected with either of Pn6A-HCH or Pn6A-TT, the injection of the two conjugates did not produce a negative effect. *See* Chu *et al.* p. 253, first column. However, this teaching would not have motivated one of skill in the art to use two different protein carriers to prevent negative interference because Chu *et al.* experienced a lack of negative effect when the protein carriers of the two conjugates were the same (*i.e.* Hib-HCH injected with Pn6A-HCH) or different (*i.e.* Hib-HCH injected with Pn6A-TT). Thus, no conclusion can be reached from Chu *et al.* that the lack of the negative effect was experienced because two different protein carriers were used. In fact, Chu *et al.* do not provide any explanation why there was no negative effect in these experiments. Chu *et al.* are concerned with increasing the antigenicity of the various conjugates. Chu *et al.* are not concerned with eliminating the negative interference associated with multivalent vaccines.

Likewise, EPA 0 497 525 does not provide any teaching of eliminating the negative interference of a multi-valent vaccine by using two or more protein carriers. Thus, given that one skilled in the art cannot conclude from Chu that using more than one protein carrier is better than using a single protein carrier, one skilled in the art would not be motivated to use more than one protein carrier in the multivalent vaccine of EPA 0 497 525. Without such motivation, a *prima facie* case of obviousness cannot be established. Accordingly, Applicant requests that the rejection of claims 1 – 12 and 14 be withdrawn.

With regard to claims 16, 17, 18 and 21, the Examiner asserts that it would have been prima facie obvious of one or ordinary skill in the art to substitute the protein Dt as shown in EPA 0 497 525 in the Hib-HCH conjugate of Chu *et al.* because Chu *et al.* teaches that a

"useful" carrier would be preferred for human use. However, Chu *et al.* do not describe what carriers are useful or non-sense. Even assuming that Dt is a "useful" carrier, a discussed above, there is nothing in Chu *et al.* that provides the motivation for one of skill in the art to use Dt and Tt together as carriers in order to reduce the negative interference associated with multivalent vaccines. Thus, Applicant requests that the rejection of claims 16, 17, 18 and 21 be withdrawn.

The Examiner also argues that, with regard to claims 1 - 24, that it would have been *prima facie* obvious to one of ordinary skill in the art to modify the conjugate composition of Chu *et al.* by adding any of the Pn-Ps-PRO conjugates of EPA 0 497 525 to provide a conjugate vaccine containing up to 23 different Pn-Ps-PRO conjugates. However, as stated above, the motivation in Chu *et al.* to make this combination is lacking. Thus, Applicant requests that this rejection be withdrawn.

CONCLUSION

With the above amendments and remarks, Applicant respectfully submits that the application is in condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of this matter, the Examiner is encouraged to contact Applicant's undersigned representative.

Respectfully submitted,

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